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## Primary Carcinoma of the Lung

### Diagnosis by Cytological Studies of Sputum and Bronchial Secretions

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A RECENT study of 200 cases of primary carcinoma of the lung that came to autopsy<sup>2,3</sup> revealed that the diagnosis usually had been made in the late stages of the disease or at autopsy. This late diagnosis of a disease which annually results in over 15,000 deaths in the United States is regrettable since thoracic surgeons are now able to remove the involved lung with "cure" in many cases if the diagnosis is established early. Consequently, attention should be centered on the early diagnosis of this disease.

The most important single factor in the diagnosis is that the physician must think of the possibility of bronchogenic carcinoma. Among the more common early respiratory symptoms are persistent cough, hemoptysis, pain in the chest and wheezing. Cough is relatively dry at first and is more productive later. Symptoms of this nature occurring in a patient, particularly in a male over 40 years of age, should immediately suggest the possibility of bronchogenic carcinoma. If the presence of this disease is suspected a thorough course of investigation should be carried out. This should include the taking of a careful history, physical examination, complete roentgenological study of the chest, and bronchoscopy. Lipiodol studies may be helpful. Often exploratory thoracotomy is necessary to establish the diagnosis.

Attention has been focused recently on a simple method of suggesting, establishing or confirming the diagnosis of primary carcinoma of the lung. Inasmuch as primary carcinoma of the lung is considered bronchogenic and the malignant cells tend to exfoliate into the lumen of the bronchus, it is logical to attempt to find these free cells in the sputum or

bronchial secretions. It is the purpose of this paper to discuss some of the more important features of this diagnostic method.

#### HISTORY

The presence of neoplastic cells in the sputum of a patient with bronchogenic carcinoma was first reported by Hampeln in 1887.<sup>4</sup> Hampeln and other early workers prepared sputum for microscopic examination in dried smears or imbedded histological sections which were usually stained by simple methods. Unlike the earlier workers, Dudgeon and Wrigley in 1935 used wet films which they fixed in Schaudinn's fluid and stained with Meyer's hemalum and eosin.<sup>1</sup> In 1944 Wandall in Denmark reported finding neoplastic cells in the sputum by using a wet film technique and staining with hematoxylin and eosin.<sup>9</sup> Herbut and Clerf reported on the adaptation to the study of bronchial secretions of the Papanicolaou technique for studying vaginal cytology.<sup>5</sup> Numerous other reports have appeared in the English, Latin-American and Russian literature.

#### METHOD OF PREPARING SLIDES

Material must be carefully obtained and slides properly prepared in order to preserve the cytologic detail essential for the recognition of malignant cells and differentiation of them from the normal cellular flora of sputum or bronchial secretions. If sputum is to be examined the patient is instructed to raise secretions from the lower part of the respiratory tree. Smears should be made immediately to avoid loss of cellular detail by autolysis. If there is to be a period of time before slides are prepared and fixed, it is best to have the sputum expectorated into jars containing 10 cc. of the fixative solution. Sputum should

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be examined in a Petri dish against a dark background. Various suspicious components of the sputum such as tissue fragments or blood flecks are selected, using a magnifying glass if necessary, and are gently smeared over two-thirds of the slide. Pressure will cause distortion during this procedure. Thick smears are not suitable for the study of cytologic detail. It is important to immerse the smears in the fixative solution while they are still wet. This fixative solution consists of equal parts of ether and 95 per cent ethyl alcohol. A paper clip attached to alternate slides will separate the smears.

Bronchial secretions obtained at bronchoscopy are treated in the same manner. Secretions should be obtained from suspicious areas of the bronchial tree for preparation of slides. If secretions are very scant all material should be saved.

We have found that after fixation for a two-hour period slides may be removed from the solution and permitted to stand, protected from dust, for at least seven days before staining. This permits mailing of slides to laboratories where trained personnel can examine the smears.

Smears are stained by the Papanicolaou technique. This method has been described in detail in the monograph of Papanicolaou and Traut on the diagnosis of uterine cancer by the vaginal smear.<sup>8</sup> It is not necessary with this technique to control the nuclear stain with microscopic observation as it is with hematoxylin and eosin.

#### CYTOLOGY OF SPUTUM AND BRONCHIAL SECRETIONS

*Nonmalignant components.* The nonmalignant components of sputum and bronchial secretions are epithelial cells, cells from the blood and cells from the reticulo-endothelial system. Epithelial cells include ciliated columnar cells from the trachea and bronchi. Squamous cells originate in the mouth, pharynx and occasionally, in areas of metaplasia in the lower part of the respiratory tree. Blood elements which may be observed include erythrocytes, polymorphonuclear leukocytes, lymphocytes, monocytes and, occasionally, megakaryocytes. The reticulo-endothelial system contributes macrophages (histiocytes) and giant cells. Macrophages may exhibit marked pleomorphism. They may be mistaken for malignant cells, particularly when they do not contain phagocytised particles. A careful and thorough study of sputum from patients suffering from various types of nonmalignant respiratory disease is a necessary prerequisite to study of smears for neoplastic cells.

*Malignant components.* Neoplastic cells found in the sputum and bronchial secretions may be classified as differentiated and undifferentiated. Differentiated neoplasms in the lung include squamous cell (epidermoid) carcinomas and adenocarcinomas. It is not always possible to assign one malignant cell to the appropriate classification when it is encountered alone. When groups of malignant cells are seen it may be possible to classify them. The average malignant cell usually is large but it may not be, particularly if it is exfoliated from anaplastic carcinomas.

The nuclear-cytoplasmic ratio is usually large and at times the nucleus may appear to be naked. The nuclei may attain excessive size. They can vary in shape, position and size, and one cell may have more than one nucleus. This variability is particularly noted when various malignant cells are compared. The chromatin is usually arranged in irregular fragments or in a coarse meshwork. Mitotic figures may be observed. Nucleoli vary in size, shape and number from one cell to another. Groups of malignant cells may be crowded together in a manner not seen in macrophages or other normal cellular components. Phagocytosis is rarely exhibited by malignant cells.

#### RESULTS OF CYTOLOGIC STUDIES

Wandall reported finding neoplastic cells in the sputum of 84 of 100 cases of bronchogenic carcinoma. Herbut and Clerf preferred to work with secretions aspirated at bronchoscopy because the specimen was less diluted with secretions from upper portions of the bronchial tree. They reported malignant cells in 46 of 57 (89 per cent) cases of proven bronchogenic carcinoma. Woolner and McDonald<sup>10</sup> reported that they were able to demonstrate neoplastic cells in 70 cases, but it is not clear in how many of their cases the diagnosis was substantiated by tissue studies nor in what percentage of proved bronchogenic carcinoma the smears were positive.

We have used this diagnostic method for 15 months, and cytologic study of 1,512 specimens from 414 patients suspected of having "carcinoma of the lung" has been carried out. Positive or suspicious cells were found in 69 cases. Pathologic confirmation of the diagnosis of carcinoma of the lung has been established in 56 cases. In 46 (82 per cent) of these 56 cases, cytologic examination revealed or suggested the presence of bronchogenic carcinoma. Sputum smears were obtained in 52 cases of proved malignant disease; in 43 (82 per cent) of these cells were found which indicated or suggested the diagnosis of carcinoma of the lung.

As diagnostic criteria were developed and perfected our efficiency improved. As with any technique many of the early mistakes were found to be avoidable. We feel that diagnostic efficiency will be increased as a result of additional experience in evaluating the appearance of malignant, as well as the normal, components of the sputum.

#### REPORT OF THREE CASES

Three cases in which malignant cells were demonstrated in the sputum and the diagnosis was later confirmed by tissue examinations, are presented.

**CASE 1.**—A white man 67 years old was hospitalized on July 31, 1947. He complained of malaise, loss of weight, difficulty with breathing and a productive cough of four months' duration. Roentgenographic examination revealed an infiltrative process along the right cardiac border (Figure 1). On August 5, examination of a specimen of sputum revealed cells which suggested the presence of malignancy (Figure 2). At bronchoscopy a polypoid tumor was found which seemed to originate from the posterior wall of the right main stem bronchus, 1 cm. below the carina. Results of study of a

biopsy specimen were negative but bronchial smears revealed malignant cells. Biopsy was repeated and the tissue revealed epidermoid carcinoma (Figure 3).

CASE 2.—A 65-year-old white man was hospitalized on December 30, 1946. He had had hemoptysis, cough, had been

raising mucus for two months and had lost weight during that time. The sputum was found to contain tubercle bacilli. On roentgenologic examination evidence of chronic bilateral inflammatory disease and a circumscribed density in the right upper lung field (Figure 4) were observed. Bronchoscopy on January 7 did not reveal abnormal findings. A

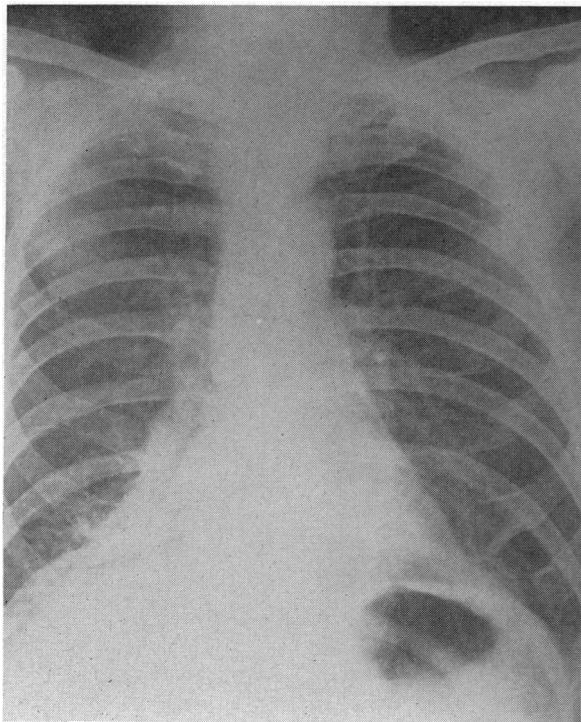


Figure 1

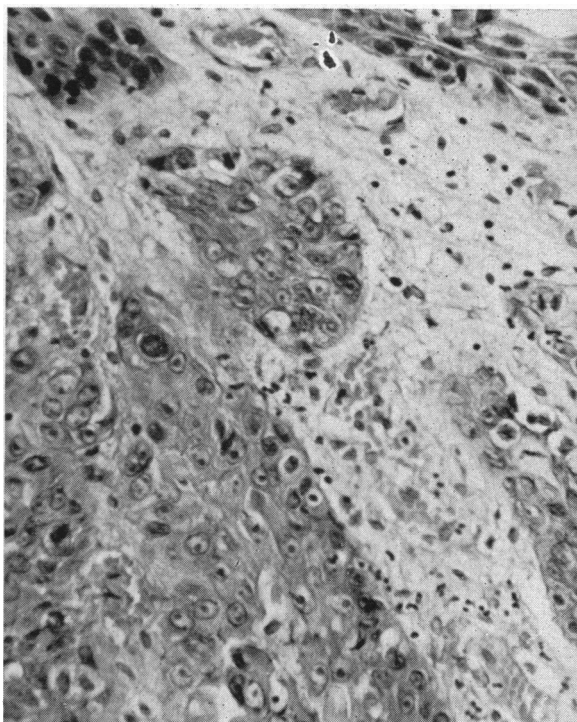


Figure 3



Figure 2

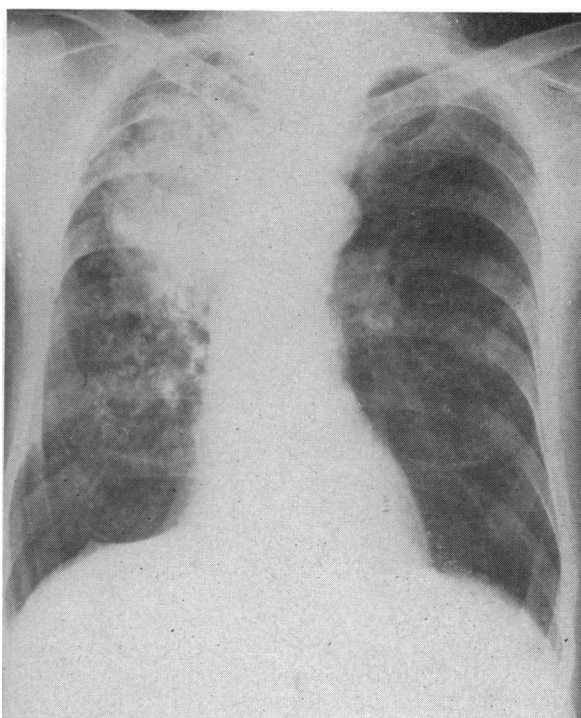


Figure 4

bronchogram revealed the presence of an obstructive lesion of the right upper lobe bronchus. In July sputum was submitted for cytologic study and was found to contain many malignant cells (Figure 5). The patient subsequently died and at autopsy an adenocarcinoma and coexistent pulmonary tuberculosis were found (Figure 6).

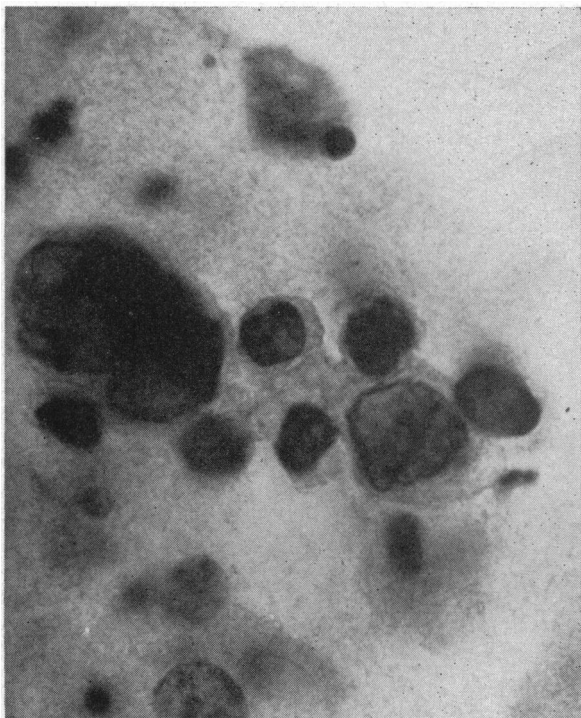


Figure 5

CASE 3.—A 61-year-old white male was first seen by one of the authors in May, 1947. He had had pleuritic pain, cough productive of a small amount of blood on several occasions and night sweats for eight months, and he had lost weight. A roentgenogram revealed evidence of atelectasis of the lingular segment of the left upper lobe (Figure 7). On May 20, examination of a sputum specimen revealed malignant cells (Figure 8). A week later bronchoscopy revealed a mass in the left upper lobe and a rigid, deformed left main stem bronchus. Left pneumonectomy was per-

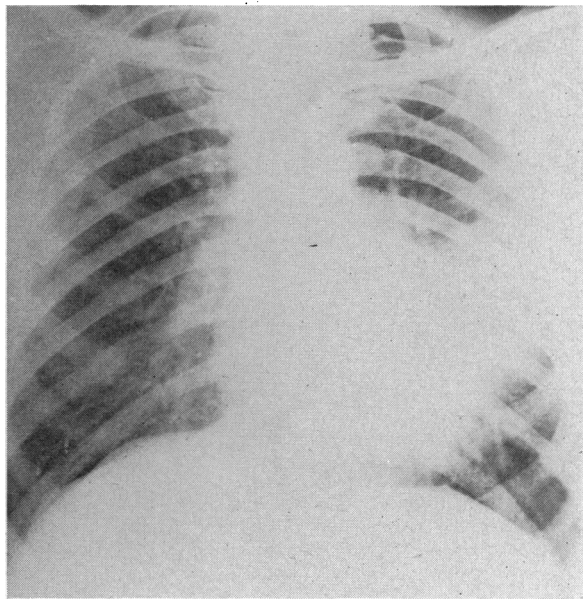


Figure 7

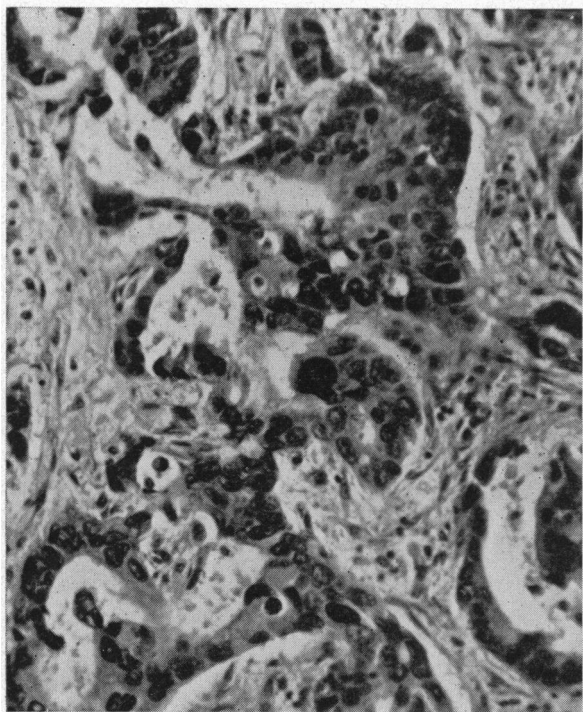


Figure 6

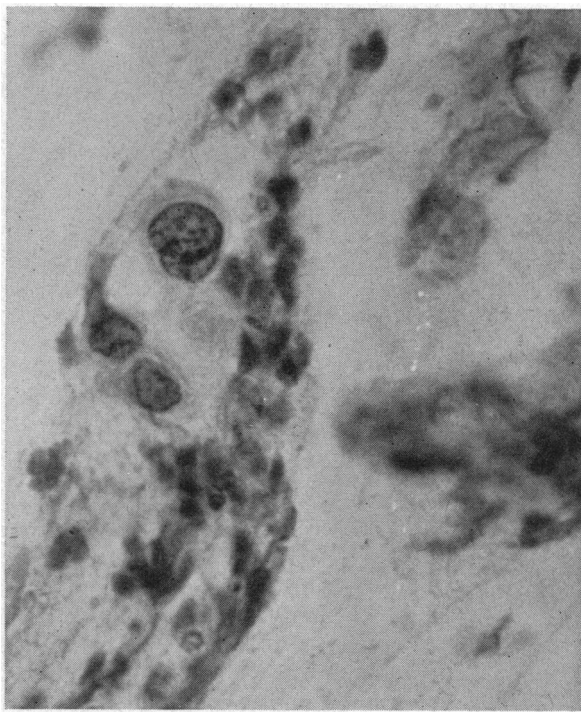


Figure 8

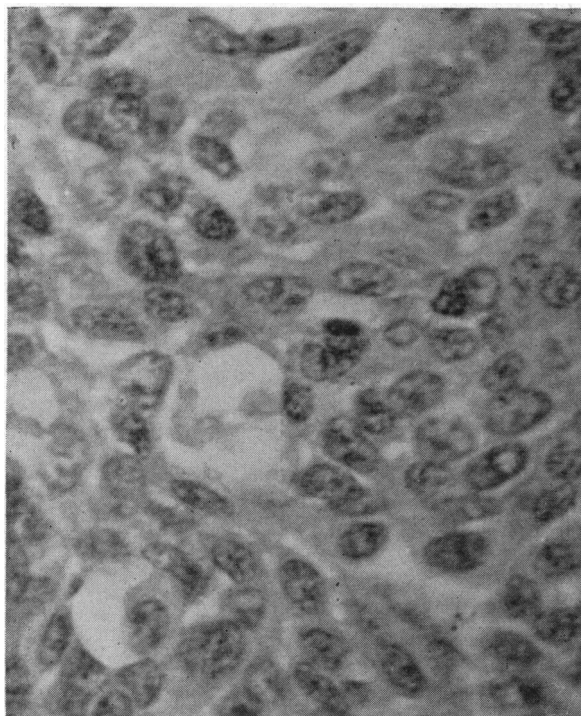


Figure 9

formed. Examination of the tissue revealed that a primary epidermoid carcinoma of the lung (Figure 9) was present.

## COMMENT

The detection of malignant cells in the sputum is a relatively simple procedure. Malignant cells can be demonstrated in the sputum or bronchial secretions in at least 80 per cent of all patients with primary carcinoma of the lung. This figure compares most favorably with the results obtained by bronchoscopy with biopsy; it is considerably higher than the figures reported in many series of cases in which bronchoscopy and biopsy are used.<sup>6</sup> Skilled bronchoscopists are available only in certain medical centers. On the other hand, sputum can be prepared for study in any city or town and submitted to experienced observers. Bronchoscopy must be carried out, however, to evaluate the location and operability of the tumor.

Most bronchogenic carcinoma arise in the major bronchi and a considerable period may elapse before they reveal themselves on the roentgenogram by producing stenosis or a recognizable mass. During that time the tumor may metastasize. It may be possible to demonstrate exfoliated malignant cells in the sputum before roentgenologic changes appear. When the tumor develops in the peripheral portion of the

lung it may produce roentgenographic changes early but the nature of these changes is difficult to evaluate. Prompt and thorough examination of the sputum, if indicated, and confirmation of the diagnosis of malignancy by cytologic study will lead to earlier and more frequent surgical treatment. This should enhance the chances for a favorable result from surgical resection.

If cancer is present, inability to demonstrate cancer cells in the sputum is frequently due to failure to examine a sufficient number of slides from an adequate series of specimens. It must be emphasized that failure to find malignant cells on smears made from a single specimen does not rule out the diagnosis of carcinoma any more than does a single negative result of examination of the sputum for tubercle bacilli exclude the possibility of tuberculosis. In our series whenever possible five or six slides made from each of five specimens were examined. At times it was found necessary to obtain more than five specimens before malignant cells were demonstrated.

## SUMMARY

Exfoliated neoplastic cells in the sputum of patients with primary carcinoma of the lung can be identified in an appreciable percentage of cases after diligent examination. The utilization of the Papanicolaou technique for the examination of sputum and bronchial secretions is outlined. Three cases in which this procedure was of value in suggesting, establishing or confirming the diagnosis of bronchogenic carcinoma are reported.

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